UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,153	07/21/2003	Yvonne M. Chen	P1469R1C1	2413

9157 7590 04/24/2006

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 04/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/624,153	CHEN ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *20-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *May 24, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I in the reply filed on March 27, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-31 are all the pending claims for this application.

Claims 20-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected groups, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on march 27, 2006.

Claims 1-19 are the claims under examination.

Information Disclosure Statement

2. The U.S and foreign patent references and the nonpatent literature references filed in the IDS of March 24, 2006 have been considered and made of record.

Sequence Compliance

3. Pursuant to 37 CFR 1.821, a sequence identifier must be provided for any amino acid sequences of four or more residues or nucleotide sequences of 10 or more nucleotides. The following omissions have been identified in the specification:

A) VNERK at p. 6, line 9

Applicants will need to provide a revised Sequence Listing, a computer readable form of the Sequence Listing and a statement. Please see the attached Notice to Comply Form, for which the Examiner has set a 3-month shortened statutory period for response.

Specification

4. Applicant should amend the cross-reference of the instant specification to indicate that the instant application is a continuation of 09/440,781, now USPN 6,632,926.

5. Applicants will need to amend the specification by providing sequence identifiers for the following sequences in addition to any other sequences that may not be properly identified:

A) VNERK at p. 6, line 9

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-19 are indefinite for reciting "antibody variant" in the claims because the exact meaning of the phrase is not clear. The term "antibody variant" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the parent antibodies are to be derivatized to yield the class of variants referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "variant" of the parent antibody is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term "antibody variant " does not appear to be clearly defined in the specification, see page 11, lines 10-35, which defines the term meaning any antibody sequence which differs from the parent antibody, the term can encompass proteins with amino acid substitutions, insertions, or deletions, antibody fragments, chemically derivatized molecules, or even antibody mimetics. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody, wherein the parent antibody is Fab-12, wherein the antibody comprises all 6 CDRs from the Fab-12, wherein the antibody comprises an amino acid insertion in the CDRH3 wherein the binding affinity for VEGF is two to ten fold greater than the Fab-12 antibody, wherein the from 1 to 30 amino acids have been inserted into CDRH3, wherein the potency in a biological assay is 20 to 50 fold greater than the Fab-12 antibody, wherein the antibody is a human or humanized antibody, wherein the CDRH3 of the antibody comprises the amino acid sequence of SEQ ID Nos 53, 54, 78, 85, 86, 89, 98, or 99, and compositions comprising such, does not reasonably provide enablement for any antibody variant of any parent antibody wherein the antibody comprises insertion into any hypervariable region wherein the binding affinity of the antibody variant is at least two or at least five fold stronger binding affinity of the parent antibody, wherein the antibody variant has a potency of at least 20 or at least 50 fold greater than the potency of the parent antibody, wherein the CDRH3 comprises SEQ ID Nos 53, 54, 78, 85, 86, 89, 98, or 99 and the other CDRs can be any amino acid sequence and compositions comprising such. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in

the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to insertion of amino acids into any hypervariable region of any antibody and obtaining a binding affinity of at least 2 to at least 5 fold greater than the parent antibody and potency of at least 20 to at least 50 fold greater than the potency of the parent antibody. In addition, the claims broadly encompass any antibody wherein the CDRH3 are SEQ ID Nos 53, 54, 78, 85, 86, 89, 98, or 99 and wherein the other 5 CDRs can be any sequence.

The specification teaches a parent antibody Fab-12 (see Figures 1A and 1B) and insertions into this antibody within the CDRH3 wherein the affinity of these antibodies are between 1 and 9.7 fold greater than the Fab-12 antibody (see Table 17) and wherein the antibodies comprise a CDRH3 sequence of SEQ ID Nos 53, 54, 78, 85, 86, 89, 98, or 99 and compositions comprising such. The specification fails to enable any antibody variant of any parent antibody wherein the antibody comprises insertion into any hypervariable region wherein the binding affinity of the antibody variant is at least two or at least five fold stronger binding affinity of the parent antibody, wherein the antibody variant has a potency of at least 20 or at least 50 fold greater than the potency of the parent antibody, wherein the CDRH3 comprises SEQ ID Nos 53, 54, 78, 85, 86, 89, 98, or 99 and the other CDRs can be any amino acid sequences and compositions comprising such.

The enablement provided in the specification is not commensurate in scope with the broadly drawn claims. The claims encompass any antibody variant wherein the antibody comprises any insertion into any hypervariable region including the CDRs of any parent antibody. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the claims which may contain any insertion into any CDR , have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue

experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. In addition, Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986). Thus, one skilled in the art would not expect insertions into just any hypervariable region to result in an antibody with the claimed properties.

The claims are broadly drawn to an antibody which has a binding affinity for a target antigen that is at least 2 to at least 5 fold greater than the affinity of a parent antibody for said antigen. The specification does not enable antibodies with such high affinity wherein the affinity is greater than 10 fold. While it is well known in the art that antibodies can be screened which have very high affinities, indeed the art has shown that sheep produce a repertoire of antibodies that are very high affinity antibodies, see Groves et al (Hybridoma 6:7-76, 1987; IDS #18), the prior art does not provide support for greatly increasing the affinity of an antibody by the claimed method.

Claims 16-19 encompass any antibodies with a CDRH3 sequence of SEQ ID Nos 53, 54, 78, 85, 86, 89, 98, or 99 and any other sequences for the other 5 CDRs. The specification does not enable any antibodies with a CDRH3 comprising SEQ ID Nos 53, 54, 78, 85, 86, 89, 98, or 99 except those wherein the other 5 CDRs are from the Fab-12 antibody. The specification does not teach that the affinity of just any

antibody can be increased by a sequence inserted into any CDRH3 comprising SEQ ID Nos 53, 54, 78, 85, 86, 89, 98, or 99.

Therefore, in view of the lack of guidance in the specification and in view of the unpredictability in the art as evidenced by Rudikoff et al, Panka et al, Amit et al, and Groves et al, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Jones et al (Nature 321:522-525, 1986; IDS #20).

a. The claims recite an antibody variant of a humanized or human parent antibody comprising an amino acid insertion of about one to about 30 or about two to about ten in or adjacent to a hypervariable region of the parent antibody and has a binding affinity for a target antigen which is at least about two to about five fold stronger than the binding affinity of the parent antibody for said antigen and about 20 to about 50 fold greater in potency in a biological assay compared to the potence of the parent, wherein at least one of the inserted residues has a net positive charge or negative charge and is lysine or arginine, wherein the insertion is adjacent to residue number 100

of the heavy chain using the Kabat numbering system and further comprising an amino acid substitution.

b. Jones et al teach a method of CDR grafting which produces an antibody that has an amino acid insertion into the CDRH3 of the heavy chain comprising a substitution of human CDR residues with mouse residues. At least one of the inserted residues is a lysine (see Figure 2a) and the inserted residues are adjacent to residue 100 using Kabat numbering system and the parent antibody is a human antibody.

Jones is silent about the increase in affinity of the produced antibody versus the parent antibody or the increase in potency in a biological assay. Therefore, it is inherent that Jones et al have produced an antibody that has an affinity for an antigen that is greater than the affinity of the parent NEWM antibody and has greater potency in a biological assay compared to the NEWM antibody. It is inherent that Jones' antibody also possesses the same structural and functional properties as those of the antibodies claimed and, therefore, Jones et al have produced an antibody that is identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibody with the antibody of Jones et al, the burden of proof is upon the Applicants to show a distinction between the structural and functional characteristics of the claimed antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

9. Claims 1-2, 4-8, 10-12 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al (Protein Engineering 6:745-754, 1993, IDS #23).

a. The claims have been described supra.

b. Lee et al teach a VL of a human antibody comprising insertions of 12-20 residues in the CDR3 region wherein at least one residue is an arginine positive charged residue (see Figure 6) and the antibody has an affinity greater than the affinity of the REI for the antigen (receptor) and has greater potency in a biological assay compared to the REI (Table 1).

10. Claims 1-8 and 10-13 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by McLane et al (Proc. Natl. Acad. Sci. USA 92:5214-5218, 1995, IDS #24).

a. The claims have been described supra.

b. McLane et al teach an antibody with an insertion into CDRH3 of the heavy chain comprising insertion of 17 amino acid residues wherein the parent antibody is a human antibody (see page 5215) and does not bind the antigen and the antibody with the inserted sequence binds the antigen (see Table 1) and the inserted sequence contains a lysine residue (see Figure 1). Thus, the antibody with the inserted sequence would bind the antigen with a higher binding affinity than the parent antibody and would have higher potency in a biological assay compared to the Fab p313 antibody thus meeting the limitation of the claims.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

LAB

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

Notice to Comply	Application No. 10/624,153	Applicant(s) CHEN ET AL.	
	Examiner Lynn Bristol	Art Unit 1643	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY